CASE REPORT

Pretreated *EGFR*^{del19}/*BRAF*^{V600E} Lung Adenocarcinoma With Leptomeningeal Disease Achieving Long-Lasting Disease Control on Osimertinib, Dabrafenib, and Trametinib: A Case Report

Corrado Orciuolo, MD,[a,*] Federico Cappuzzo, MD,[a] Lorenza Landi, MD,[b] Blerina Resuli, MD,[a] Silvia Carpano, MD,[a] Antonello Vidiri, MD,[c] Simonetta Buglioni, MS,[c] Chiara Mandoj, MD,[c] Gennaro Ciliberto, MD,[c] Gabriele Minuti, MD[b]

[a]*Division of Medical Oncology 2, IRCCS National Cancer Institute Regina Elena, Rome, Italy*
[b]*Clinical Trials Center: Phase 1 and Precision Medicine, IRCCS National Cancer Institute Regina Elena, Rome, Italy*
[c]*IRCCS Regina Elena National Cancer Institute, Rome, Italy*

Received 13 February 2023; revised 14 June 2023; accepted 24 June 2023
Available online - 30 June 2023

ABSTRACT

Oncogene-addicted NSCLC inevitably becomes resistant to targeted therapy by developing acquired resistance through on- or off-target mechanisms, potentially detectable by liquid biopsy. We present the first reported case of a patient with pretreated *EGFR*^{del19}/*BRAF*^{V600E} lung adenocarcinoma and symptomatic leptomeningeal metastasis obtaining durable clinical benefit on osimertinib, dabrafenib, and trametinib treatment.

Keywords: NSCLC; Case report; Targeted therapy; Osimertinib; Resistance

Introduction

Osimertinib, a third-generation EGFR tyrosine kinase inhibitor (TKI), is the standard front-line treatment for patients with metastatic NSCLC harboring activating *EGFR* mutations. However, all tumors eventually become resistant by developing different molecular mechanisms, including *EGFR C797S* mutation, *EGFR* and *MET* amplifications, and *KRAS, PIK3CA, HER2, and BRAF* mutations.[1] De novo *BRAF* mutations are detected in 2% to 6% of advanced NSCLC cases, whereas approximately 3% of *EGFR*-mutant NSCLCs acquire them at osimertinib failure. Preclinical studies have proven that a combination of *BRAF* and *MEK* inhibitors with osimertinib could be successful to overcome resistance in NSCLC harboring co-occurrence of *EGFR* and *BRAF*^{V600E} mutations.[2] Leptomeningeal metastasis (LM) is a devastating and life-threatening complication in advanced NSCLC, with a median life expectancy of approximately 90 days.[3] Here, we report a case of long-lasting disease control on dabrafenib, trametinib, and osimertinib treatment in a patient with lung adenocarcinoma and LM carrying *EGFR* and *BRAF*^{V600E} mutations.

*Corresponding author.

Disclosure: The authors declare no conflict of interest.

Address for correspondence: Corrado Orciuolo, MD, *Istituto di Ricovero e Cura a Carattere* Scientifico (IRCCS) National Cancer Institute Regina Elena, Rome, Regina Elena Institute, Via Elio Chianesi, 53, Roma Capitale, RM 00144, Italy. E-mail: corrado.orciuolo@gmail.com

Cite this article as: Orciuolo C, Federico C, Lorenza L, et al. Pretreated *EGFR*^{del19}/*BRAF*^{V600E} lung adenocarcinoma with leptomeningeal disease achieving long-lasting disease control on osimertinib, dabrafenib, and trametinib: a case report. *JTO Clin Res Rep*. 2023;4:100545.

ISSN: 2666-3643
https://doi.org/10.1016/j.jtocrr.2023.100545

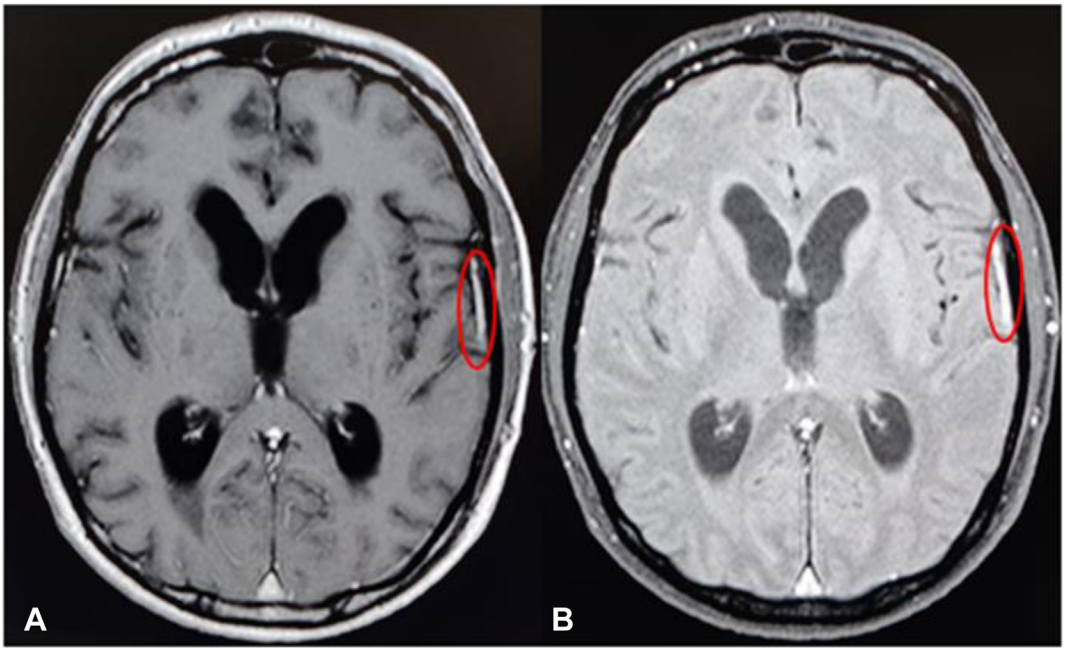

Figure 1. Baseline brain MRI (June 2021). T1W1 sequence after contrast medium infusion (*A*) and FLAIR sequence in axial planes (*B*) illustrate leptomeningeal dissemination characterized by focal epicortical meningeal enhancement at the left parietal area. FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance imaging.

Case Presentation

A 56-year-old man, a never-smoker, was diagnosed with advanced lung adenocarcinoma. Computed tomography (CT) scan performed in April 2019 revealed bone, brain, and adrenal metastases. At baseline, real-time polymerase chain reaction revealed a classical *EGFR* mutation in exon 19 (*EGFR E746_A750del*). Immunohistochemistry tested negative for ALK, ROS1, and programmed death-ligand 1. In May 2019, the patient started first-line osimertinib 80 mg daily in response to a CT scan performed in September 2019. During TKI treatment, a next-generation sequencing (NGS) on liquid biopsy (LB) using the Illumina MiSeq platform (Illumina, San Diego, CA) confirmed the original *EGFR* mutation and the appearance of a concomitant *BRAF* mutation (*c.1799T>A/p.V600E*). Because of persistent radiologic response, the patient continued osimertinib until disease progression occurred in April 2021. At that time, the patient was treated with platinum-based chemotherapy for three cycles. Unfortunately, in June 2021 a brain magnetic resonance required for evaluation of clinical and cognitive impairment revealed LM with hydrocephalus (Fig. 1*A* and *B*). To control neurologic symptoms, the patient underwent right shunt surgery, with modest improvement in neurologic symptoms. At that point, considering both performance status and molecular profile and according to literature data supporting the use of concomitant *EGFR/BRAF/MEK* inhibitors, the patient was informed about the potential utility of this strategy and agreed by signing an informed consent. Therefore, in July 2021, the combination of dabrafenib 75 mg twice daily and trametinib 1 mg once daily was added to osimertinib treatment, with evidence of complete response on brain magnetic resonance imaging (Fig. 2). After 2 months of treatment, the patient

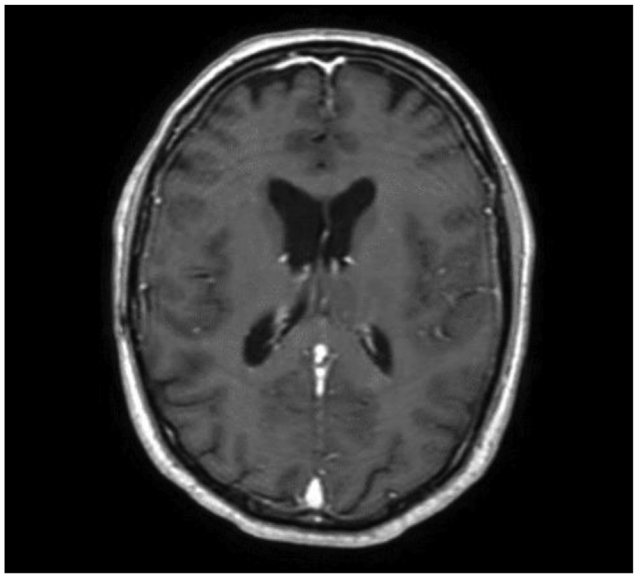

Figure 2. Brain MRI performed in February 2022 underlying brain complete response. MRI, magnetic resonance imaging.

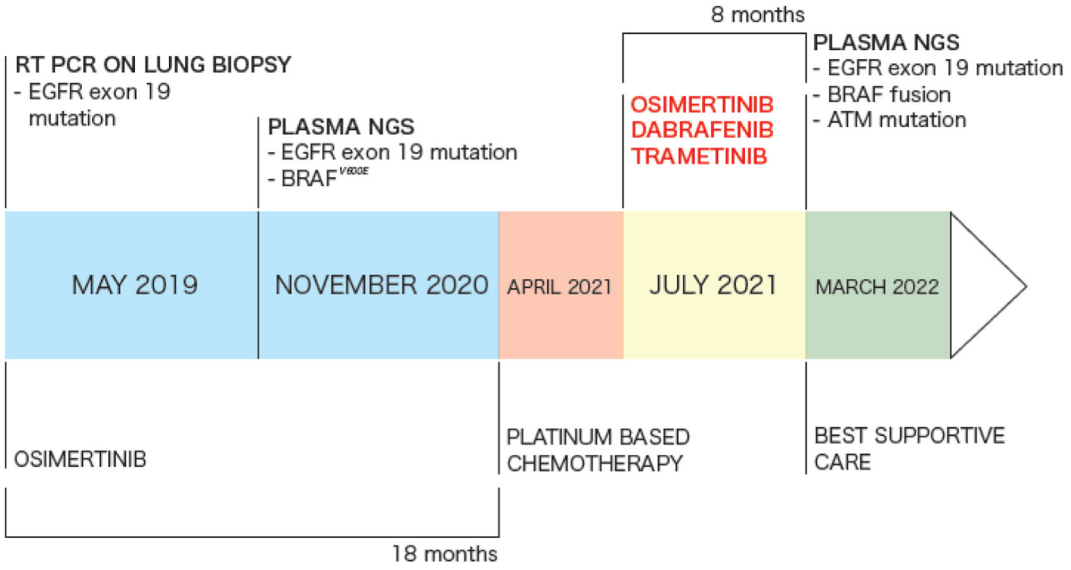

Figure 3. Timeline of the whole course of treatment. NGS, next-generation sequencing; RT PCR, reverse transcription polymerase chain reaction.

developed grade 1 interstitial lung disease requiring temporary discontinuation of medical treatment and initiation of systemic steroids. In March 2022, the disease progressed within the peritoneum without evidence of brain progression. Cytologic evaluation of peritoneal effusion tested negative for neoplastic cells. A new LB was performed using a different NGS test (FoundationOne, Foundation Medicine Inc., Cambridge, MA), the result of which revealed the original *EGFR* mutation coupled with the new onset of *BRAF-TRIM24* fusion and *ATM* mutation. In April 2022, because of rapid clinical deterioration, the patient was referred to a palliative care specialist (Fig. 3).

Discussion

Approximately 3% to 5% of patients with advanced NSCLC present LM, and for these individuals, life expectancy is in the range of 1 to 3 months. However, the availability of new potent and highly-CNS penetrant agents such as osimertinib improved the prognosis of selected cases of LM. In the phase 1 BLOOM study, patients with LM were treated with high-dose osimertinib after progressing on a previous EGFR TKI.[4] The median progression-free survival exceeded 6 months and the median overall survival reached 11 months. In $BRAF^{V600E}$-positive NSCLC, the incidence of LM remains unknown and the impact of BRAF TKIs alone or in combination with MEK inhibitors deserves further investigation. In a previous case report, a patient with $BRAF^{V600E}$ NSCLC and LM had a radiologically and clinically confirmed response to a BRAF inhibitor. Here, we reported a case of a patient with $EGFR^{ex19}/BRAF^{V600}$ comutant lung cancer with LM, experiencing long-lasting disease control with osimertinib, dabrafenib, and trametinib. In the context of oncogene-driven NSCLCs such as *EGFR* mutants, acquired resistance (AR) is the inevitable consequence of the therapeutic pressure of a targeted agent. Activation of the *BRAF* pathway, mainly represented by $BRAF^{V600E}$ mutation is responsible for AR to osimertinib in less than 5% of cases, whereas co-occurrence of classical de novo *EGFR* and *BRAF* mutations seems even rare if it exists. Unfortunately, in our case, the lack of an NGS test precluded the definition of the exact molecular status at diagnosis. $BRAF^{V600E}$ mutation was detected on circulating tumor DNA when the disease was still responding to osimertinib, highlighting how LB could be a noninvasive tool able to monitor response to the treatment and capture early molecular changes potentially responsible for AR. In fact, as we know from literature data, progression occurred earlier in blood tests than in CT scans. Preclinical data and anecdotal evidence suggested a potentially relevant activity of triplet therapy with *EGFR/BRAF/MEK* TKIs in the case of acquired *EGFR* and *BRAF* comutation. Ribeiro et al.[5] described a remarkable response to such triple therapy in a patient with metastatic lung cancer harboring $EGFR^{del19}$ and $BRAF^{V600E}$ mutations. In our case, after the failure of triple therapy, the disease progressed within the peritoneum, and LB identified a *BRAF* fusion, an emerging mechanism of resistance in *EGFR*-mutant NSCLC or *BRAF*-mutant melanoma. Moreover, peritoneal progression occurred without any symptoms or radiologic signs of brain progression, and this fact underlines the probable link to AR.

Conclusions

In conclusion, our case provides the first evidence of durable disease control lasting approximately 8 months with osimertinib, dabrafenib, and trametinib in a patient with advanced *EGFR*-addicted lung adenocarcinoma with symptomatic LM failing osimertinib by developing a *BRAF* mutation. This case also highlights the role of LB as a powerful diagnostic tool in detecting targetable driver events and monitoring clonal evolution during treatment.

CRediT Authorship Contribution Statement

Corrado Orciuolo: Investigation, Data curation, Writing – original draft.

Federico Cappuzzo: Supervision.

Lorenza Landi: Writing – review and editing.

Gabriele Minuti: Conceptualization, Writing – review and editing.

Silvia Carpano: Visualization.

Blerina Resuli: Visualization.

Simonetta Buglioni: Resources, Visualization.

Antonello Vidiri: Resources, Visualization.

Chiara Mandoj: Resources, Visualization

Gennaro Ciliberto: Visualization.

Acknowledgments

The authors thank the patient who has signed a consent to data processing for research purposes. We thank the Fondazione Ricerca Traslazionale (FoRT) for the support.

References

1. Oxnard GR, Hu Y, Mileham KF, et al. Assessment of resistance mechanisms and clinical implications in patients with EGFR T790M-positive lung cancer and acquired resistance to osimertinib. *JAMA Oncol*. 2018;4:1527–1534.
2. Vojnic M, Kubota D, Kurzatkowski C, et al. Acquired BRAF rearrangements induce secondary resistance to EGFR therapy in EGFR-mutated lung cancers. *J Thorac Oncol*. 2018;14:802–815.
3. Remon J, Le Rhun E, Besse B. Leptomeningeal carcinomatosis in non-small cell lung cancer patients: a continuing challenge in the personalized treatment era. *Cancer Treat Rev*. 2017;53:128–137.
4. Yang JCH, Kim SW, Kim DW, et al. Osimertinib in patients with epidermal growth factor receptor mutation-positive non-small-cell lung cancer and leptomeningeal metastases: the BLOOM study. *J Clin Oncol*. 2019;38:538–547.
5. Ribeiro M, Knebel FH, Bettoni F, et al. Impressive response to combination dabrafenib, trametinib, and osimertinib in a metastatic EGFR-mutant/ BRAF V600E lung adenocarcinoma patient. *NPJ Precis Oncol*. 2021;5:5.